Current Use and Developments Needed for Optimal Design in Pharmacometrics: A Study Performed Among DDMoRe's European Federation of Pharmaceutical Industries and Associations Members

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INTRODUCTION

Methods and software tools for optimal design in nonlinear mixed effect models (NLMEM) have been developed and proposed for a decade[1]. They are based on the evaluation and optimisation of the Fisher information matrix, whose inverse is a lower bound of the expected variance of estimation. Since the first optimal design tools for population pharmacokinetics[2], at least 5 software tools have been developed and new versions[3-5] with improvements have been made available on a regular basis by several academic groups. They are mainly applied for pharmacokinetic-pharmacodynamic (PKPD) studies. Present tools do not yet allow optimization of adaptive designs for these models, although prior information on models and parameter values are needed and adaptive designs are increasingly used and promising in drug development[6,]. Before developing this capacity we conducted a study among the 10 drug companies which are members of the Drug Disease Model Resources (DDMoRe) European consortium[7] to identify current practices, shortcomings and expectations.

STUDY ON USE OF OPTIMAL DESIGN IN PHARMACOMETRICS

In 2011, the Drug Disease Model Resources (DDMoRe) consortium was approved as one of the Innovative Medicines Initiative (IMI) projects of the European Union with the objective of developing a drug-disease model library and an open-source interoperability framework[7]. This project associates 9 academic groups, 6 small and medium sized enterprises, and 10 pharmaceutical companies that are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA). One of the work packages within DDMoRe is responsible for development and integration of new tools, among others also for adaptive optimal designs in PKPD using nonlinear mixed effect models (NLMEM).

The working group members and authors of this article designed a questionnaire for this study. It was sent to each EFPIA representative within DDMoRE in October 2011. Each

representative was then in charge to ask one to three scientists within the company to respond to the questionnaire, mostly to those indeed involved in designing PKPD studies. The detailed questionnaire is available as Supplementary Figure S1. Responders first stated how clinical trials were generally designed, by simulations, heuristic approaches and/or optimal design. The main body of the survey was composed of two parts, part 1: state of the art on the use of optimal design methods in industry, part 2: requests for future developments using adaptive optimal design.

RESULTS

Results were obtained in November 2011 from all the 10 member companies of the DDMoRe consortium (100% response rate): AstraZeneca, GSK, Lilly, Merck Serono, Novartis, Novo Nordisk, Pfizer, Roche, Servier, UCB Pharma.

Current Situation

Part 1 of the study investigated the current situation. The first question showed that optimal design software tools in NLMEM are being used by nearly all companies (9/10), mostly during Phase 1 and 2 for Pharmacokinetics (PK)/Pharmacodynamics (PD), sometimes for biopharmaceutical studies later in development in special populations: paediatric patients, patients with renal or hepatic impairment and the elderly. All currently available software tools were used among the respondents. Here a list of the programs and their frequency of usage: PFIM (University Paris Diderot & INSERM, 6/9), POPED (University of Uppsala, 3/9), POPDES (University of Manchester, 3/9), POPT (University of Otago, 3/9).

Optimal design approaches are used for a variety of investigations and design complexity (Table 1). Interestingly, optimal design is often used in early clinical phases (I and II), and less in phase III; one responder suggested that there is a lack of models able to handle complex endpoints encountered in later phases. Current limitations were expressed in free text which is available as Supplementary Table S1. The most common

limitation was the need to change software when moving from estimation to design, showing a strong need for more integrative/global approaches/tools. Several companies were concerned about the limited models currently implemented in most optimal design software tools and suggested to add more flexibility. Overall, the perceived impact of optimal design was generally considered quite important, with potentially wider applications suggested in the industry.

Adaptive Designs and further developments

Adaptive design in NLMEM is of high priority for most companies with a median of 4, on a scale of 0 to 5, with 4 companies quoting a 5 (very useful). The answers to specific needs were: (i) start from prior information (8/9), (ii) design optimisation after each new cohort (8/9), (iii) use stopping rules (6/9). One company highlighted that adaptive design is not possible in therapeutic areas where endpoints are attained slowly while recruitment is fast.

The importance of new developments in design tools was graded on a scale from 0 to 5. Results are given in Table 2 and show that the priorities are: (i) handling of continuous covariates, (ii) dealing with data below quantification limit, (iii) robustness across models, and (iv) design for discrete outcome data also in combination with continuous data. Additional expectations were expressed in text (Supplementary Table S1).

CONCLUSION

This study illustrates that optimal design methodology has been quickly adopted within the industry, especially in early phases where PKPD is more important. This is study further highlights expected improvements in interoperability between optimal design and estimation software and in statistical capabilities of the optimal design methodology. A smooth workflow between estimation, model evaluation and design will be facilitated on the DDMoRe platform. It should be noted that we did not perform a comprehensive

systematic review of the use of optimal design software tool in NLMEM in drug companies outside of DDMoRe, therefore the presented results may be biased.

Another outcome of the study is the high priority was given to further development of adaptive optimal design (AOD) in NLMEM with optimisation not only of sampling times but of other design variables, e.g. doses (Table 1). Initial work on AOD in population PK demonstrated its feasibility[8], but the approach is not yet fully studied nor implemented in any available software. Those developments will only address some of the issues of the complexity of adaptive design in drug development. For instance, adaptive dose-ranging studies analysed by nonlinear models without random effects, are already being optimised[6]. Also, as pharmacometrics has increased its scope beyond population PK, design tools for more complex models and for other types of data, especially discrete data, are now needed. Academic groups are actively working on those topics and are sharing their results to translate progress into new software tools, but collaborations with statisticians involved in other aspects of the complex issues in adaptive designs are also increasingly needed. Optimal design enriches clinical trial simulation, and both will work in concert to improve model-based drug development in the pharmaceutical industry.

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Table 1: Current use of optimal design software tools for the n=9 EFPIA companies, out of the 10 of DDMoRe, presently using this approach.

	Yes
Type of investigations	
Design evaluation	7
Design optimisation	8
Power evaluation	6
Complexity of designs	
Dose/input optimisation	6
Sampling windows in designs	7
Several group of elementary designs	7
Bayesian/robust approaches	5
Complex error models	3
Inter-occasion variability	3
Covariates	5
Multi-response models	4

Table 2: Expectations of n=10 EFPIA companies of DDMoRe regarding capabilities of a new optimal design software

	Median	Range
Accepts continuous covariates	5	3-5
Handles data below quantification limit	4	2-5
Handles robustness across models	4	2-5
Handles discrete data	4	1-5
Handles jointly continuous and discrete data	4	1-5
Handles repeated time to event (rtte) data	3	1-5
Predicts shrinkage	3	1-5
Provides standard errors for individual parameters	3	1-5
Provides choice of several optimality criteria	3	1-5
Handles jointly continuous and rtte data	3	1-3

Scale from 0 to 5.